Direct-to-Consumer Broadcast Advertisements for Pharmaceuticals: Off-Label Promotion and Adherence to FDA Guidelines

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BACKGROUND: Direct-to-consumer (DTC) advertisements for prescription drugs in the United States are regulated by the Food and Drug Administration (FDA). Off-label promotion, or the advertisement of a drug for an indication not approved by the FDA, is prohibited. Our objective was to examine the presence of off-label promotion in broadcast DTC ads and to assess their adherence to FDA guidelines mandating fair balance in presentation of risks and benefits and prohibiting misleading advertisement claims.

METHODS: All English-language broadcast DTC ads for prescription drugs that aired in the United States from January 2015 to July 2016 were obtained from AdPharm, an online collection of healthcare advertisements. Ad length was measured and adherence to FDA guidelines was assessed for several categories: key regulatory items, indicators of false or misleading ads, and indicators of fair balance in presentation of risks and benefits.

RESULTS: Our sample included 97 unique DTC ads, representing 60 unique drugs and 67 unique drug-indication combinations. No ads described drug risks quantitatively, whereas drug efficacy was presented quantitatively in 25 (26%) ads. Thirteen (13%) ads, all for diabetes medications, suggested off-label uses for weight loss and blood pressure reduction. The most commonly advertised drugs were indicated for the treatment of inflammatory conditions ($n = 12$; 18%), diabetes or diabetic neuropathy ($n = 11$; 16%), bowel or bladder dysfunction ($n = 6$; 9%), and infections or allergic reaction ($n = 6$; 9%). More than three-quarters ($n = 51$; 76%) advertised drugs to treat chronic conditions.

CONCLUSIONS: Few broadcast DTC ads were fully compliant with FDA guidelines. The overall quality of information provided in ads was low, and suggestions of off-label promotion were common for diabetes medications. The impact of current DTC ads and off-label marketing on patient and prescriber decisions merits further scrutiny.

KEY WORDS: direct-to-consumer advertising; pharmaceutical promotion; off-label promotion; off-label marketing; FDA guideline adherence.

INTRODUCTION

Since 1985, the US Food and Drug Administration (FDA) has allowed direct-to-consumer (DTC) advertising of drugs.[1] Proponents argue that DTC advertising provides valuable information and empowers patients to make medical decisions, while critics claim that it undermines the patient–physician relationship, leads to inappropriate prescribing practices, and increases healthcare costs.[2–4] Research has shown that DTC advertising for prescription drugs increases patient demand, prescribing, and sales for the advertised drugs.[3,5–8] In 2015, spending on DTC ads in the US reached $5.6 billion.[9] A small number of drugs make up most of the spending, and brand-name prescription drugs that are more costly than generic alternatives tend to be the most highly advertised and promoted.[10–12] Television DTC ads are becoming a more prominent means of marketing; it is estimated that US citizens watching an average amount of television may see nine drug ads per day, or up to 30 h of DTC ads each year.[13,14]

Although the FDA regulates the labeling and advertising of prescription drugs and requires drug companies to submit all promotional materials to the Office of Prescription Drug Promotion (OPDP), in light of capacity and resource constraints, the agency does not review every ad.[4] Federal regulations prohibit ads that are false or misleading with respect to a drug's risks or benefits and require all promotional claims to be supported by evidence. In addition, all DTC advertising, regardless of the media, must present a fair balance between risk and efficacy information. While print advertisements must state all of the risks in the drug's FDA-approved label, broadcast DTC ads are only required to include the "major" risks, as long as (1) those risks are communicated in audio, and (2) the ad provides a source for consumers to access the FDA-approved labeling for the drug ("adequate provision").[5,14,15] Lastly, the FDA has traditionally taken the position that the Food, Drug, and Cosmetic Act restricts the promotion of an unapproved indication ("off-label" promotion), and federal

regulations explicitly prohibit DTC ads from even suggesting an off-label use.[5,16–18] Pharmaceutical companies have used the First Amendment to challenge certain restrictions on off-label marketing. Recent federal court cases have permitted companies to promote off-label indications to physicians, thereby calling into question the FDA's authority to regulate off-label marketing, even with respect to DTC advertising.[19–21]

Previous studies of print, television, and online advertisements have found that many do not adhere to the regulations and guidelines set forth by the FDA.[9,10,22–26] However, the most recent study was based on advertisements aired from 2008 to 2010, examining the most strongly emphasized claim in each of 84 prescription drug ads and finding that of these, 55% were potentially misleading and 2% were false.[24] To our knowledge, few studies have examined contemporary adherence of DTC ads to the regulations and guidelines set forth by the FDA, and none have examined the prevalence of suggestions of off-label promotion, which is particularly important given that regulatory standards for off-label promotion are currently being challenged in the courts. In the present study, we assess the degree to which recently aired DTC ads for prescription drugs adhered to FDA regulations and guidelines, and we examine whether off-label use was suggested.

METHODS
Data Source and Sample

We conducted a descriptive analysis of television DTC ads for prescription drugs aired in the US between January 2015 and July 2016. We obtained the ads in August 2016 from AdPharm, an online database of healthcare and pharmaceutical advertisements.[27] The gallery includes ads for prescription and over-the-counter medications. AdPharm is updated daily, and major television networks are monitored regularly for new content. We limited our search to English-language DTC advertisements for prescription medications and removed all duplicate ads prior to analysis, such that the ad was represented only once in our sample. Duplicate ads were those that had the same length and script.

Data Collection Instrument

We created an ad data collection instrument with 40 items, of which 26 were derived from federal regulations or FDA guidance for broadcast ads,[4,15,28] and 14 described additional characteristics of the ad or the drug advertised. Of these 26 items, 11 were identified as key regulatory requirements, seven were chosen as indicators of ads that were potentially false or misleading, and eight were chosen as indicators of ads that might be lacking in fair balance between presentation of risks and benefits. Of the 14 descriptive items, 10 were developed to characterize ad appeal, including the age and sex of the protagonist, whether there were real patients, whether there were celebrity patients, and whether the ad referenced savings

or insurance coverage. We also examined whether there were abbreviations or animation/mascots, because the FDA is conducting research on whether animation impacts recall or perception of risk and benefit information.[19] We collected the drug's trade and generic names, length of the ad, and initial date aired from the AdPharm website.[20] Four items collected from the FDA website[17] were chosen to describe the advertised drugs: whether the drug carried a black box warning, the initial FDA approval date for the drug, the approved indication(s) for use, and the type of condition treated by the drug. We defined a chronic condition as one lasting more than 1 year, an intermediate condition as lasting less than 1 year, and an acute condition as lasting less than 1 month. All other items were abstracted by viewing the ads. All items with justification for their inclusion and/or references can be found in the Online Supplementary Table.

Data Abstraction

Regulations require broadcast DTC ads to communicate "major risks" in the audio (or both audio and visual), along with adequate provision for viewers to find full risk information. Because there is no guidance on how to determine which risks are major, we assessed whether the ads included the information in the "Highlights of Prescribing" page of the drug's FDA-approved label, which is the first page. The Highlights page contains the following categories of information: contraindications and limitations of use, warnings and precautions (including black box warnings), and adverse events. We examined whether all items in each of these categories were presented in the broadcast ad. We also acquired the most recently approved product label for each drug at the time the commercial was aired from the FDA website,[17] characterizing all suggested indications for use as FDA-approved (on-label) or off-label. In addition, we consulted the drug label to determine whether comparative claims made in the ads were mentioned in the label. If quantitative information was included in the ads, we characterized the type of data as relative risk reduction (RRR), absolute risk reduction (ARR), both, or neither.

Evaluation and Reliability

One author (KK) abstracted the information described above for all DTC ads, and a second author (JK) validated data abstraction for a random 20% sample. We measured reliability for binary variables by overall percentage agreement. For two continuous variables—time spent discussing risk and number of risk claims—we calculated percentage disagreement by dividing the median difference between the raters by the average risk time or average number of risk claims, respectively. Two authors (KK, JSR) jointly examined quantitative efficacy statements to determine whether they were presented as ARR, RRR, both, or neither, or whether the type of data was indeterminate. Overall percentage agreement for binary variables was 95%, while agreement was 98% for time spent describing risks and 86% for number of risk claims.

Statistical Analysis

We used descriptive statistics to characterize adherence to FDA guidelines, including key regulatory items and off-label promotion, indicators of potentially false or misleading ads, and indicators of ads potentially lacking in fair balance. All analyses were performed using Microsoft Excel (Microsoft Corp., Redmond, WA).

RESULTS

Study Sample

One hundred fifty-one DTC advertisements were identified, including 97 unique ads; 54 ads were excluded as duplicates. Among unique ads, 60 drugs were represented. Four drugs were advertised for more than one indication: adalimumab (Humira) was advertised for five indications, apixaban (Eliquis) for two, onabotulinumtoxin A (Botox) for two, and pregabalin (Lyrica) for two. Thus, there were 67 unique drug–indication combinations.

Among the 67 ads with unique drug–indication combinations, the most commonly advertised drugs were indicated for the treatment of inflammatory conditions ($n = 12$; 18%), diabetes or diabetic neuropathy ($n = 11$; 16%), bowel or bladder dysfunction ($n = 6$; 9%), and infections or allergic reaction ($n = 6$; 9%). Other indications advertised included sexual dysfunction, psychiatric or neurological disorders, cardiovascular disease, and lung disease (Table 1).

More than three-quarters of unique drug–ad combinations ($n = 51$; 76%) advertised drugs to treat chronic conditions, whereas 12 (18%) were for intermediate conditions and four (6%) for acute conditions. Forty percent ($n = 27$) advertised drugs carrying black box warnings.

Ad Characteristics

The median advertisement length was 60 s (interquartile range [IQR], 60–90 s; Table 2). We used the ages and genders of the protagonists in each ad as a marker of the probable target population. Most of the protagonists were young ($n = 36$; 37%) or middle-aged ($n = 27$; 28%). The majority of ads had female protagonists ($n = 43$; 44%) or included both male and female protagonists ($n = 35$; 36%). Four (4%) ads did not contain a human protagonist. Sixty percent ($n = 58$) of advertisements made reference to potential savings on or payment for the drug. Seven ads (7%) included a notice with instructions on reporting side effects and adverse events to the FDA, a practice that is required for print but not broadcast advertisements.

Off-Label Promotion

All advertisements included an approved use for the drug (Table 3). In addition to communicating an approved indication, 13% ($n = 13$), which comprised five unique diabetes

Table 1 Characteristics of the Prescription Drugs for which Broadcast Direct-to-Consumer Ads Aired in the United States from January 2015 to July 2016

Characteristic	Unique drug–indication combination ($n = 67$)
Indication*	No. (%)
Inflammatory conditions[†]	12 (17.9)
Diabetes[‡]	11 (16.4)
Bowel/bladder dysfunction[§]	6 (9.0)
Infections/allergic reaction[‖]	6 (9.0)
Sexual dysfunction[¶]	4 (6.0)
Psychiatric/neurological[#]	7 (10.4)
Cardiovascular**	7 (10.4)
Lung[††]	6 (9.0)
Other[‡‡]	8 (12.0)
Condition type treated*	No. (%)
Chronic	51 (76.1)
Intermediate	12 (17.9)
Acute	4 (6.0)
Black box warning	No. (%)
Yes	27 (40.3)
No	40 (59.7)
Initial drug approval year	No. (%)
2012 and later	29 (43.3)
2007–2011	8 (11.9)
2002–2006	17 (25.4)
1997–2001	6 (9.0)
Prior to 1997	7 (10.4)

*Drugs that were advertised for >1 indication in the same ad were classified for the indication that accounted for the preponderance of use
[†]Rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, inflammatory bowel disease
[‡]Type 1 diabetes, type 2 diabetes, diabetic neuropathy
[§]Irritable bowel syndrome with diarrhea, overactive bladder, irritable bowel syndrome with constipation & chronic idiopathic constipation, opioid-induced constipation
[‖]Allergic reaction/anaphylaxis, infection prophylaxis post-chemotherapy, flu, toenail fungus, hepatitis C
[¶]Erectile dysfunction, erectile dysfunction with benign prostatic hyperplasia, dyspareunia
[#]Depression, bipolar depression, Alzheimer's disease, multiple sclerosis, insomnia
**Anticoagulation, heart failure, high cholesterol
[††]Chronic obstructive pulmonary disease, asthma, small cell lung cancer, smoking cessation
[‡‡]Acne, chronic dry eye, fibromyalgia, gastroesophageal reflux disease, chronic migraine, osteoporosis, birth control

medications, suggested non-FDA-approved—or off-label—uses, all of which were for weight loss and/or reduction in systolic blood pressure.

Key Regulatory Requirements

All ads included the established drug name or ingredient information with the proprietary name; 95% ($n = 92$) included the proprietary and established names/ingredient information for the same amount of time, and 97% ($n = 94$) included the established name/ingredient information in type font that was at least half as large as the type font used for the proprietary name. Only 20% ($n = 20$) of ads used the established name in the audio portion of the ad, which is not required but suggested. Seventy-eight percent of ads ($n = 76$) described all risk information in audio, while 22% ($n = 21$) had at least one risk in running text only. While the FDA requires at least one form of adequate provision in each broadcast ad, all but one ad ($n = $

Table 2 Characteristics of the Broadcast Direct-to-Consumer Ads for Prescription Drugs that Aired in the United States from January 2015 to July 2016 ($n = 97$)

Item	No. (%)
Portrays patient(s)/contains patient testimonial*	89 (92)
Ad contains a real patient taking the drug[†]	14 (16)
Ad contains a celebrity patient taking the drug[†]	8 (9)
The patient in the ad speaks[†]	55 (62)
Age of protagonist in the ad[‡]	
Young	38 (39)
Middle	27 (28)
Older	7 (7)
More than one age group represented	21 (22)
No human protagonist	4 (4)
Sex of protagonist[‡]	
Female	43 (44)
Male	15 (15)
Both	35 (36)
No human protagonist	4 (4)
Makes reference to savings on drug/insurance coverage	58 (60)
Uses an abbreviation for medical condition	37 (38)
Contains animation or mascots	21 (22)
Ad includes a notice with instructions on reporting side effects to FDA	7 (7)

*Four ads did not contain human protagonists. Of the five Viagra ads included in this analysis, only one had a male patient present in the commercial

[†]Parameter addressed only if preceding criteria were met; percentage is based on the number of ads meeting preceding criteria. For example, the percentage value for the ads containing a real patient is based on the number of ads in which patients were present (n = 89)

[‡]The protagonists for Namenda and Namzaric were the patient caretakers, and for all five Viagra ads, the protagonists were the female partner

96; 99%) included all forms of adequate provision suggested by the FDA: a toll-free phone number to call for drug labeling, web address to access labeling, reference to a print ad for the drug, and a statement indicating that the viewer's physician could provide more information. One ad did not have a toll-free phone number but included all other suggested forms of adequate provision.

Table 3 Key Regulatory Elements Described in the Broadcast Direct-to-Consumer Ads for Prescription Drugs that Aired in the United States from January 2015 to July 2016 ($n = 97$)

Item	No. (%)
Naming	
Established drug name/ingredient info accompanies proprietary name*	97 (100)
Established and proprietary names/ingredient info displayed for the same amount of time*	92 (95)
Established name/ingredient info is used in audio	19 (20)
Established name/ingredient info appropriately sized*	94 (97)
Adequate provision	
Provides toll-free number to call for labeling[†]	96 (99)
Provides web address to access labeling[†]	97 (100)
Reference to a print ad for the drug[†]	97 (100)
States that physician can provide more information[†]	97 (100)
Off-label promotion and major risk information	
Communicates an approved use*	97 (100)
Markets off-label[‡]	13 (13)
Major risks/limitations of use presented in audio as opposed to running text only*	76 (78)

*These items are specifically required by the FDA
[†]These items are suggested by the FDA to fulfill the "adequate provision" requirement
[‡]This is specifically prohibited by the FDA

Indicators of Potentially False or Misleading Ads

Only 26% ($n = 25$) of ads contained quantitative efficacy information (Table 4). Of these, 12% ($n = 3$) provided ARR, 4% ($n = 1$) provided RRR, 24% ($n = 6$) provided both ARR and RRR, 52% ($n = 13$) provided quantitative information that was neither ARR nor RRR, and 8% (n = 2) contained data that could not be classified, such as "In our largest study, when added to metformin, people lost on average up to 6.2 pounds." None of the commercials contained quantitative information regarding risks or side effects. Thirty-three percent ($n = 27$) of ads mentioned all contraindications and limitations of use in the drug's FDA-approved label, 59% ($n = 57$) mentioned all adverse events, and 53% ($n = 50$) included all warnings and precautions. Every ad for a drug that carried a black-box warning in its label communicated this safety warning.

Forty (41%) ads mentioned clinical studies or clinical evidence, though only three of these (8%) provided a citation for the study or the data. Fifteen (15%) ads made comparisons to other therapies, and of these, 12 (80%) made claims that were supported by information in the advertised drug's FDA-approved label.

Indicators of Ads Potentially Lacking Fair Balance

The median percentage of time spent describing risks was 45% (IQR, 39–52; Table 5). The median percentage of time

Table 4 Indications of Potentially False or Misleading Information Described in the Broadcast Direct-to-Consumer Ads for Prescription Drugs that Aired in the United States from January 2015 to July 2016 ($n = 97$)

Item	No. (%)
Provides quantitative information for efficacy/benefit	25 (26)
Absolute risk reduction*	3 (12)
Relative risk reduction*	1 (4)
Both absolute risk reduction and relative risk reduction*	6 (24)
Neither absolute risk reduction nor relative risk reduction*	13 (52)
Indeterminate*	2 (8)
Quantitative information is provided for risks	0 (0)
Ad mentions all contraindications and limitations of use[†]	27 (33)
Ad mentions all adverse events	57 (59)
Ad mentions all warnings and precautions (including boxed warnings)[‡]	50 (53)
Mentions studies/clinical evidence	40 (41)
Citation is provided for clinical evidence*	3 (8)
Makes comparative claims to other therapies	15 (15)
Comparative info is included in the labeling*	12 (80)
There is running text on the screen during risk info that is not related to risk	77 (79)
Risk information is accompanied by distracting visuals	97 (100)

*Parameter addressed only if preceding criteria were met; percentage is based on the number of ads meeting preceding criteria. For example, the percentage value for the ads containing a real patient is based on the number of ads in which patients were present (89)

[†]Fourteen ads were for drugs that did not have any contraindications or limitations of use; percentage is determined from drugs that did have contraindications/limitations of use

[‡]Two ads were for drugs that did not have any warnings or precautions; percentage is determined from drugs that did have warnings or precautions

Table 5 Indications of Fair Balance Required in the Broadcast Direct-to-Consumer Ads for Prescription Drugs that Aired in the United States from January 2015 to July 2016 (n = 97)

Risk Time	Median (IQR)
Percentage time spent describing risks (%)*	45 (39–52)
Percentage time spent on topics other than risk (%)*	58 (45–61)
Number of risk claims*	16 (12–23)
Time spent/risk claim*	2 s (1.6–2.3)
Item	No. (%)
Volume is the same during benefit and risk sections*	97 (100)
Background music is the same during benefit and risk sections*	96 (99)
Announcer is the same for benefit and risk information*	56 (58)
Ad ends on a statement of†	
Benefit	38 (39)
Risk	17 (18)
Neither	42 (43)

*These items are related to the "fair balance" requirement from the FDA, and these specific examples of fair balance are provided as examples in guidance documents
†The FDA recommends that risk information be put at the beginning or end of broadcast ads, where viewers are most likely to remember it

spent on other forms of communication, such as description of benefits or drug indication, was 55% (IQR, 48–61). The median number of risks described in each ad was 16 (IQR 12–23), with a median of 2 s spent per risk claim (IQR 1.6–2.3). Forty-two percent of ads (n = 41) used a different announcer for risk and benefit information, all of the ads had the same audio volume level for the presentation of risk and benefit information, and all but one (n = 96; 99%) had the same background music playing through the description of the risk and benefit information. Thirty-nine percent of ads (n = 38) ended on a statement of benefit, 18% (n = 17) ended on a statement of risk, and 43% (n = 42) ended with neither risk nor benefit information. Ads that ended with neither benefit nor risk information ended with cost information or another neutral statement. In all ads, presentation of risk information was accompanied by distracting visuals, such as frequent scene changes or characters dancing and singing, and 79% (n = 77) had running text on the screen during the audio risk presentation that was not related to risks, such as "See our ad in *Weight Watchers*." To illustrate representative examples of the types of quantitative data and slogans used in broadcast DTC ads, Table 6 includes selected excerpts from the ads.

DISCUSSION

Our study examined the degree to which prescription drug television DTC advertisements that aired between January 2015 and July 2016, adhered to regulations and FDA guidelines and whether there were suggestions of off-label promotion. Our findings demonstrate that the quality of information in DTC television ads is low: none described drug risks quantitatively; only one-quarter described drug benefits quantitatively; and suggestions of off-label promotion were common for diabetes medications. Though proponents argue that

Table 6 Illustrative Efficacy Statements/Ad Slogans from Broadcast Direct-to-Consumer Ads for Prescription Drugs that Aired in the United States from January 2015 to July 2016 (n = 97)

Drug	Efficacy statement/Ad slogan
Victoza	"Victoza is not approved for weight loss. In our largest study, when added to metformin, people lost on average up to 6.2 pounds."
Stelara	"Most people using Stelara saw 75% clearer skin, and the majority were rated as cleared or minimal at 12 weeks."
Botox	Running text: "Botox prevents on average 8 to 9 headache days and migraine/probable migraine days a month (versus 6 to 7 for placebo)."
Botox	Screen shows text that says: "Adults using Botox had fewer accidents than those who did not," and graph shows that placebo had 4 daily leakage episodes and Botox patients had 3 at week 12.
Jublia	Narrator: "Fight it with Jublia!" Celebrity: "Oh, epic moves, big J," said as the Jublia mascot fights a cartoon toenail fungus. Narrator: "Fight it! Getting ready for your close-up? Ask your doctor if Jublia is right for you."
Chantix	Running text: "In studies, 44% of CHANTIX users were quit during weeks 9 to 12 of treatment (compared to 18% on sugar pill)."
Prolia	"I can tell you Prolia is proven to help protect bones from fracture, but the real proof? My doctor said Prolia helps my bones get stronger. Are your bones getting stronger?"
Movantik	"You sound like you're ready for the movan-talk. Opioids block pain signals, but they can also block activity in the bowel, causing constipation. Movantik can help reduce constipation caused by opioid pain medications."
Neulasta	"In a key study, Neulasta reduced the risk of infection from 17% to 1%, a 94% decrease."
Opdivo	Running text: "In a clinical trial, Opdivo reduced the risk of dying by 41% compared to chemotherapy (docetaxel). Half the Opdivo patients were alive at 9.2 months versus 6 months for chemotherapy (docetaxel)." Narrator: "It's not every day something this big comes along—a chance to live longer." "A chance to live longer," is written in lights on skyscrapers.
Tamiflu	"Prescription Tamiflu can help you get better 1.3 days faster. That's 30% sooner." Running text: "In studies, Tamiflu helped shorten the time adults were sick by 1.3 days (30%)."
Trulicity	Running text: "Trulicity is not a weight loss drug. In studies, people who lost weight lost 2–6 lbs on average."
Brilinta	"Brilinta worked better than Plavix and even reduced the chances of dying from another one…I will take Brilinta today, tomorrow, and every day for as long as my doctor tells me. Don't miss a day of Brilinta."
Eliquis	"I accept that I'm not 21. I accept I'm not the sprinter I was back in college. I even accept that I live with a higher risk of stroke due to Afib, a type of irregular heartbeat not caused by a heart valve problem. But I won't accept giving it less than my best, so if I can go for something better than warfarin, I will. Eliquis. Eliquis reduced the risk of stroke better than warfarin. Plus, it had less major bleeding than warfarin. Eliquis had both. That really mattered to me."
Entresto	"For people with heart failure, tomorrow is not a given. But Entresto is a medicine that helps make more tomorrows possible. In the largest heart failure study ever, Entresto helped more people stay alive and out of the hospital than the leading heart failure medicine."
Farxiga	"And although it's not a weight loss or blood pressure drug, Farxiga may help you lose weight and may even lower blood pressure when used with certain diabetes medicines."
Humira	"This is my body of proof. Proof of less joint pain and clearer skin. This is my body of proof that I can fight psoriatic arthritis from the inside out with Humira…It's proven to help relieve pain, stop further joint damage, and clear skin in many adults."

Table 6. (continued)

Drug	Efficacy statement/Ad slogan
Invokana	"Imagine loving your numbers. Discover once-daily Invokana. It's the #1 prescribed SGLT2 inhibitor that works to lower A1C, and it's proven to lower A1C better than Januvia…And while it's not for lowering systolic blood pressure or weight loss, it may help you with both."
Linzess	"Linzess is thought to help calm pain-sensing nerves and accelerate bowel movements." Simultaneous running text: "This was seen in animal studies and the relevance to humans is unknown."
Osphena	"I can't believe I'm admitting this on national TV, but someone had to. After menopause, sex became extremely painful. I spoke to my doctor. She recommended I try Osphena. It treats moderate to severe painful sex due to menopause…Let's open the dialogue. Ask your doctor about Osphena. Tell them Patty sent you."
Pradaxa	Screen shows red fish that represent blood cells traveling through water-filled pipes. "Don't just go with the flow. Go with Pradaxa, the only blood thinner that lowers your risk of stroke better than warfarin and has a specific reversal treatment."
Viagra	Narrator: "About half of men over 40 have some degree of erectile dysfunction." Running text: "Data from Massachusetts Male Aging Study. Of 1290 respondents, 52% reported some degree of erectile dysfunction (ED)."

DTC advertising is educational and empowering for consumers,[2–4] our findings suggest that the information provided is unreliable and potentially misleading. The promotion of off-label indications, poor quality of information, distracting risk presentations, and the fact that risks are never quantified could distort the perception of benefit and risk information.

We found that DTC ads frequently contained information that could be considered misleading, which is consistent with prior research.[9,10,22–26] In a previous study, Faerber et al. examined 84 prescription drug advertisements and found that, of the most emphasized claims in each ad, 43% were objectively true, 55% potentially misleading, and 2% false.[24] Though in our study we did not utilize the same methods to identify potentially misleading information, we did find that the quality of information presented, particularly the quantitative data, was low. For instance, the following are efficacy statements from two ads: "Victoza is not approved for weight loss. In our largest study, when added to metformin, people lost on average up to 6.2 pounds;" and "Most people using Stelara saw 75% clearer skin, and the majority were rated as cleared or minimal at 12 weeks." Both claims are vague and difficult to interpret, providing conflicting descriptions of findings. While we found potentially misleading information in the broadcast ads in our sample, we did not identify any claims that were blatantly false. Kaphingst et al. analyzed 23 television ads from 2001 and found that only 1 of 23 ads presented risk information in a quantitative way; none of the ads in our sample presented risks in quantitative terms.[22] Lastly, another interesting finding was that 60% of ads referenced methods of payment and potential savings. Though drug coupons may defray the cost of brand-name drugs for patients in the short term, these offers are typically time-limited. Moreover, the societal costs of using drug coupons may be significant, as

patients with drug coupons are foregoing the opportunity to use less expensive alternatives.[29]

In December 2016, the FDA issued warning letters to the makers of Toujeo (insulin glargine injection) and Otezla (apremilast), citing television ads that included misleading representations of risk. The FDA stated that ads for both drugs included distracting scenes and music as well as running text on screen during the risk presentation, many of which were present in the ads we studied, and all of which are discouraged by FDA guidance,[28] as they impair the viewer's ability to absorb risk information.[30,31] These concerns were justified by recently published research suggesting that when DTC ads list severe side effects along with those that are most frequent, consumer perceptions of the overall risk severity are diluted.[32] Due to budget constraints, it might be unrealistic for the FDA to review all television commercials for prescription drugs before they are aired. However, it would be helpful if there were clearer and more detailed regulations and guidance for DTC broadcast ads, particularly with respect to providing quantitative risk information, along with better FDA enforcement of current guidance. Moreover, the FDA could consider charging a "user" fee to ensure there are sufficient resources to hire personnel that can review each ad prior to its air date.

Our findings regarding off-label promotion have not been previously demonstrated. Suggestions of off-label use, a practice that has been expressly prohibited in prescription drug DTC advertising, occurred in 13% of ads in our sample. All of these ads marketed drugs indicated for the treatment of type 2 diabetes, and suggested potential benefits of use, including weight loss and blood pressure reduction; the drugs include canagliflozin (Invokana), liraglutide (Victoza), dapagliflozin (Farxiga), empagliflozin (Jardiance), and dulaglutide (Trulicity). For example, the off-label promotion for dapagliflozin claims: "And although it's not a weight loss or blood pressure drug, Farxiga may help you lose weight and may even lower blood pressure when used with certain diabetes medicines." In March 2015, the consumer advocacy group Public Citizen sent a letter to the FDA citing off-label marketing in print advertisements for five type 2 diabetes drugs,[27] four of which we also identified in our study. To date, the FDA has not issued warning letters to the manufacturers of these drugs for off-label marketing. While we cannot explain our findings, perhaps once a drug in a certain class is marketed off-label, the others may seem inferior unless they also suggest off-label benefits. Moreover, if one company starts suggesting off-label uses and is not issued any warning or fine, other companies with similar drugs are at a disadvantage if they do not do the same.

There are important limitations of our study to consider. First, FDA regulations and guidelines for broadcast DTC ads are not always clearly defined. For example, broadcast advertisements are required by regulations to present only the major risks in the commercial as long as they meet the adequate provision requirement by providing a source for viewers to access the full drug labeling.[15] However, the criteria for

determining which risks are most important are vague. Therefore, we focused our study on how many ads included all of the information in the following categories from the drug's approved label: contraindications and limitations of use, warnings and precautions, and adverse events. Second, the assessment of DTC ads is potentially subjective. However, we used a standardized protocol for assessing ads and found excellent inter-rater reliability using our data collection instrument. Lastly, the interpretation of the FDA guidelines for DTC ads can potentially be considered subjective. By creating clearer, more objective requirements, the FDA could better regulate broadcast DTC advertising.

Overall, we found that few ads were fully compliant with FDA guidelines for DTC advertising, and that the quality of information presented in broadcast DTC ads for prescription drugs was low. Data were rarely provided to support benefit claims, the risks were never quantified, and off-label promotion occurred. Taken together, these findings have important implications for patients and clinicians. Broadcast DTC advertising could lead patients to make healthcare decisions and request certain expensive, brand-name medications based on ads containing low-quality and incomplete information. It has been shown that DTC advertising for prescription drugs increases patient demand for those drugs, which include a disproportionate number of more expensive brand-name formulations. Moreover, this increase in patient demand leads to increased prescribing and sales of the advertised drugs.[3,5–8]

Our findings are similar to previous reports, indicating that the quality of DTC advertising has not improved since it was first studied. This may be due to the lack of enforcement of DTC advertising requirements. It has been suggested that the FDA review television commercials for prescription drugs prior to their release to ensure that ads are more informative for the public.[14] By enacting such a program and by enforcing more objective requirements for DTC advertisements, the FDA could better protect consumers. In addition, the impact of off-label marketing via DTC ads on patient and prescriber decisions merits further study.

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